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Palladium-catalyzed intramolecular carboborylation of 1,3-diene and synthesis of ABCD ring of communesins

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CITATION:

Tsukano, Chihiro ...[et al]. Palladium-catalyzed intramolecular carboborylation of 1,3-diene and synthesis of ABCD ring of communesins. *Organic & Biomolecular Chemistry* 2019, 17(7): 1731-1735

ISSUE DATE:

2019-02-21

URL:

<http://hdl.handle.net/2433/243175>

RIGHT:

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Organic & Biomolecular Chemistry

COMMUNICATION

Development of Palladium-Catalyzed Carboborylation and Synthesis of Communesins ABCD Ring

Received 00th January 20xx,
Accepted 00th January 20xx

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DOI: 10.1039/x0xx00000x

www.rsc.org/

A palladium-catalyzed carboborylation has been developed for the synthesis of iminoindolines with a quaternary carbon centre. This method was applied to a substrate bearing several functional groups to afford a complex iminoindoline, which was subsequently converted into a model communesins ABCD ring compound via an intramolecular Friedel–Crafts-type reaction.

Communesins A and B are alkaloids originally isolated from the mycelium of a *Penicillium sp.* strain stuck to the marine alga *Enteromorpha intestinalis* (Figure 1).¹ Their structures have been elucidated by spectroscopic analyses, including NMR spectroscopy (¹H NMR, ¹³C NMR, NOESY) and high-resolution mass spectrometry (HRMS), with the structures of nine congeners disclosed to date.² These natural products are structurally characterized by two *N,N*-aminal moieties and two contiguous quaternary carbon stereocentres in a common septacyclic skeleton. Communesins A and B show cytotoxicity against P388 lymphocytic leukaemia cells (ED₅₀: 3.5 and 0.45 µg/mL, respectively),¹ while communesins D–F exhibit potent insecticidal activity towards silkworms (LD₅₀: 300, 80, and 80 µg/g, respectively).² Owing to their interesting structures and biological activities, and low supply from natural sources, communesin alkaloids are good synthetic targets. Furthermore, synthetic studies on these complex natural products are important for developing new synthetic methods.³ Various research groups have reported the synthesis of communesin alkaloids.⁴ Qin, Weinreb, and Funk independently achieved the racemic total synthesis of communesin F.⁵ Furthermore, Ma *et al.* reported the asymmetric total syntheses of communesins A, B, and F.^{6e,f} Recently, Movassaghi, Yang, and Chen elegantly accomplished the asymmetric total synthesis of communesin F based on a late-stage heterodimerization followed by aminal exchange, Ir-catalyzed asymmetric intermolecular cascade cyclization, and an asymmetric organocatalyzed coupling of

two oxinodes.^{6a–c} We are also interested in this unique structure, and have investigated new synthetic strategies for constructing this class of alkaloids.⁷

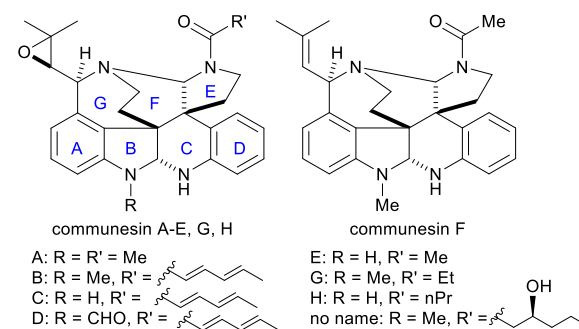


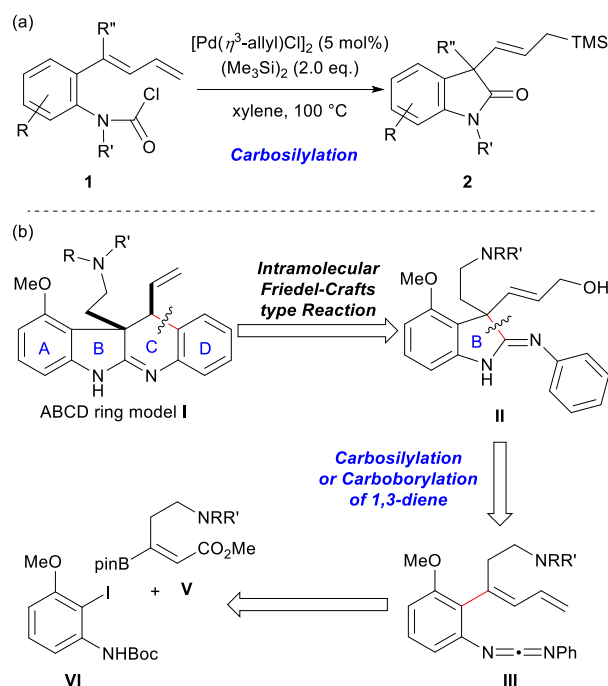
Figure 1 Structures of communesins.

During our studies, we have developed a carbosilylation of carbamoyl chloride **1**, which contains a 1,3-diene, to synthesize 3,3-disubstituted oxindoles **2** (Scheme 1a).⁸ In this reaction, an oxindole is formed along with construction of a quaternary carbon centre. This reaction could be applied to construct the ABCD ring of communesins, which bears a quaternary carbon centre. Furthermore, if a carbodiimide is employed in this transformation instead of a carbamoyl chloride, an iminoindoline bearing an amidine moiety would be obtained. To verify this idea, ABCD ring model **I** was used as a synthetic target (Scheme 1b). It was intended that the C ring would be constructed using an intramolecular Friedel–Crafts-type reaction from iminoindoline **II**. Iminoindoline **II** would be synthesized from carbodiimide **III**, which would, in turn, be accessed from iodoaniline derivative **VI** and vinyl boronic ester **V** through a Suzuki coupling. To date, the carbosilylation and carboborylation of dienes with carbodiimides has not been reported, although Mori and Yu have described an intramolecular Ni-catalyzed carbostannylation and carboborylation of 1,3-dienes bearing aldehydes through bismetallation.^{9–11} This study was initiated by investigating intramolecular carbometallation using simple 1,3-diene **3** bearing a carbodiimide as the model substrate.

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Electronic Supplementary Information (ESI) available: Experimental protocols, characterization data and NMR spectra. See DOI: 10.1039/x0xx00000x



Scheme 1 (a) Carbosilylation and (b) synthetic approach to ABCD ring model I based on carbosilylation or carboborylation.

Initially, carbodiimide **3** was treated with hexamethyldisilane ((Me₃Si)₂, 2 equiv.) and [Pd(η³-allyl)Cl]₂ (5 mol%) in xylene at 100 °C following a previously established carbosilylation method⁸ (Table 1, entry 1). The reaction gave desired iminoindoline **4** in 12% yield, along with a significant amount of 6π electrocyclic product **5**. To suppress this undesired side reaction, different reaction temperatures were investigated. At 80 °C, the yield of iminoindoline **4** was improved to 60%, although the formation of **5** was not completely suppressed (entry 2). Increasing the amount of catalyst to 10 mol% did not affect the product yields (entry 3). In contrast, at 60 °C the reaction gave iminoindoline **4** and 6π electrocyclic product **3** in 55% and 33% yields, respectively (entry 4). These results indicated that carbosilylation of **3** was the major process at 80 °C, while 6π electrocyclization of **3** was preferred at 100 °C, and formation of the desired iminoindoline **4** was slowed at 60 °C. Other Pd catalysts, including Pd(OAc)₂, Pd(PPh₃)₄, and Pd(II) acetylacetonate (Pd(acac)₂) were also examined, but the desired iminoindoline **4** was not detected or obtained in low yields under these conditions (entries 5, 7, and 8). Adding 1,1,3,3-tetramethylbutyl isocyanide¹² (TMBI) was also not effective (entry 6). We next attempted reactions using Ni and Pt catalysts, including bis(1,5-cyclooctadiene)nickel(0) (Ni(cod)₂), Ni(PPh₃)₄, NiCl₂(PPh₃)₂, PtCl₂(cod), Pt(PPh₃)₄, and Pt(CH₂=CH₂)(PPh₃)₂. However, these reactions gave 6π electrocyclization product **5** in 27%–87% yields along with small amounts of urea **6** because the desired carbosilylation did not occur (entries 9–14).

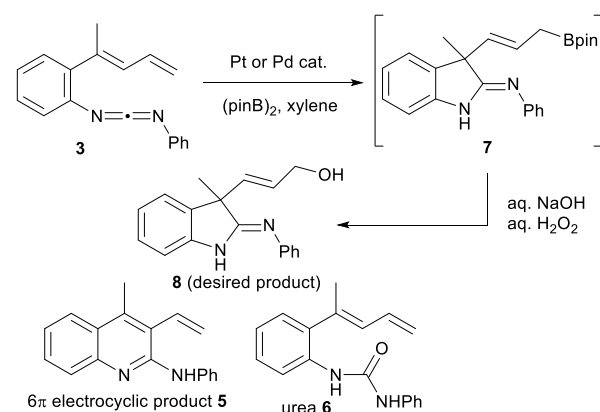
Table 1 Formation of iminoindoline **2** via carbosilylation.

entry	catalyst	temp.	yield	4	5	6
1	[Pd(η ³ -allyl)Cl] ₂	100 °C	12%	42%	–	–
2	[Pd(η ³ -allyl)Cl] ₂	80 °C	60%	26%	–	–
3	[Pd(η ³ -allyl)Cl] ₂ ^a	80 °C	55%	29%	–	–
4	[Pd(η ³ -allyl)Cl] ₂	60 °C	41%	33%	–	–
5	Pd(OAc) ₂	80 °C	7%	73%	–	–
6	Pd(OAc) ₂ /TMBI	80 °C	trace	39%	10%	–
7	Pd(PPh ₃) ₄	80 °C	–	43%	4%	–
8	Pd(acac) ₂	80 °C	–	63%	–	–
9	Ni(cod) ₂	80 °C	–	27%	19%	–
10	Ni(PPh ₃) ₄	80 °C	trace	78%	16%	–
11	NiCl ₂ (PPh ₃) ₂	80 °C	trace	56%	trace	–
12	PtCl ₂ (cod)	80 °C	–	66%	–	–
13	Pt(PPh ₃) ₄	80 °C	–	73%	–	–
14	Pt(CH ₂ =CH ₂)(PPh ₃) ₂	80 °C	–	87%	–	–

^a 10 mol% of Pd catalyst used instead of 5 mol%. Ac = acetyl, TMBI = 1,1,3,3-tetramethylbutyl isocyanide, acac = acetylacetonate, cod = 1,5-cyclooctadiene.

As the undesired 6π electrocyclization proceeded under thermal conditions, a lower temperature was required to suppress this side reaction and selectively form iminoindoline **4**. However, even at 60–80 °C, carbosilylation competed with 6π electrocyclization and the yield of the desired iminoindoline **4** remained moderate. Therefore, we investigated a carboborylation using bis(pinacolato)diboron ((pinB)₂), because oxidative addition of (pinB)₂ to Pd(0) species proceeds at a lower temperature than that of (Me₃Si)₂.¹⁰ The carboborylation of **3** would give allylboronic ester **7**, which would be too unstable to isolate (Table 2). Therefore, the products were treated with H₂O₂ and aq. NaOH to convert them into iminoindoline **8**. When carbodiimide **3** was treated with (pinB)₂ (2 equiv.) and Pt catalyst (5 mol%), including PtCl₂(cod), Pt(CH₂=CH₂)(PPh₃)₂, and Pt(PPh₃)₄ at 50–80 °C, desired iminoindoline **8** was not observed (entries 1–3). In these cases, a significant amount of 6π electrocyclic product **5** and a small amount of urea **6** were obtained. In contrast, Pd catalysts including bis(dibenzylideneacetone)palladium(0) (Pd(dba)₂), [Pd(η³-allyl)Cl]₂, and Pd(OAc)₂ were effective for the formation of iminoindoline **8** through carboborylation with suppressed 6π electrocyclization because their reactions proceeded at 50 °C (entries 4–6). In particular, the reaction with Pd(OAc)₂ gave desired iminoindoline **8** in 87% yield (entry 6). Therefore, Pd(OAc)₂ at 50 °C in xylene were the best conditions for carboborylation of a 1,3-diene bearing carbodiimide for iminoindoline construction.

Table 2 Formation of iminoindoline **8** via carboborylation.

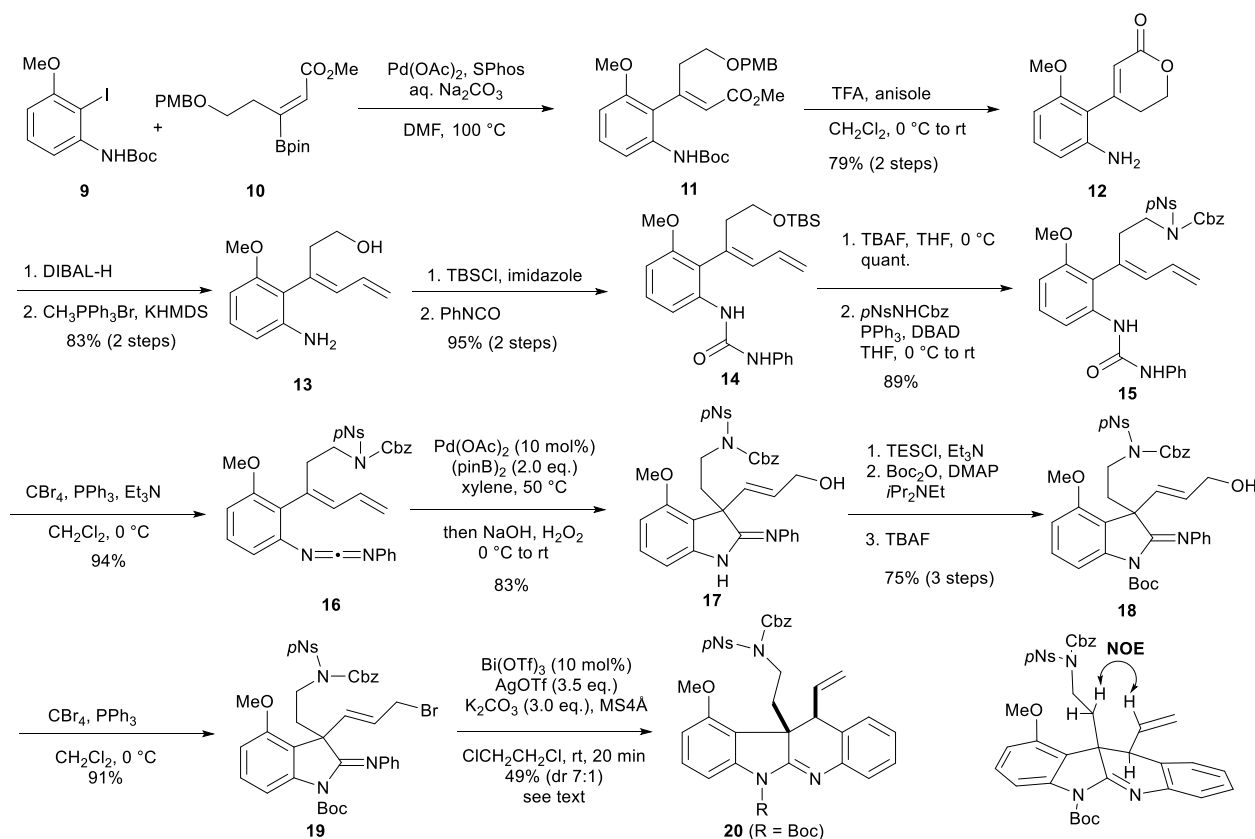


entry	catalyst	temp	yield	8	5	6
1	PtCl ₂ (cod)	50–80 °C	–	79%	–	–
2	Pt(CH ₂ =CH ₂)(PPh ₃) ₂	50–80 °C	–	54%	14%	–
3	Pt(PPh ₃) ₄	50–80 °C	–	51%	8%	–
4	Pd(dba) ₂	50 °C	49%	7%	–	–
5	[Pd(η ³ -allyl)Cl] ₂	50 °C	77%	trace	–	–
6	Pd(OAc) ₂	50 °C	87%	1%	–	–

cod = 1,5-cyclooctadiene, dba = dibenzylideneacetone.

After establishing the optimal reaction conditions for carboborylation using a carbodiimide, we focused our attention on preparing the model tetracyclic ABCD ring **1** (Scheme 1, R = *p*-nosyl (pNs), R' = benzyloxycarbonyl (Cbz), compound **20**) for communesin synthesis. Our synthesis

started with the Suzuki coupling of a known aryl iodide **9**¹³ and vinylboronic ester **10**¹⁴ using a catalytic amount of Pd(OAc)₂ and dicyclohexyl(2',6'-dimethoxy-[1,1'-biphenyl]-2-yl)phosphine (SPhos) (Scheme 2).¹⁵ Treatment of coupling product **11** with trifluoroacetic acid (TFA) and anisole gave lactone **12** in 79% yield through the removal of *p*-methoxybenzyl (PMB) and *t*-butyloxycarbonyl (Boc) groups, followed by lactonization. DIBAL-H reduction of lactone **12** gave an unstable hemiacetal that could readily form imines through inter- or intramolecular reactions. Therefore, the hemiacetal was immediately converted to diene **13** by Wittig olefination. Silylation of the primary alcohol followed by treatment with phenylisocyanate gave urea **14**, which was then converted to compound **15** through TBS group removal and Mitsunobu reaction with *p*NsNHCbz. Treatment of **15** with dehydration conditions gave carbodiimide **16** in 94% yield. With carbodiimide **16** in hand, we applied the developed conditions to access iminoindoline **17** (Scheme 2). While 10 mol% of Pd(OAc)₂ was required for this carboborylation to reach completion, the desired iminoindoline **17** was successfully obtained in 83% yield after oxidative treatment. To avoid undesired side reactions through the nucleophilic addition of amidine nitrogen, a three-step protecting group manipulation from compound **17** was essential to obtain Boc-protected iminoindoline **18** in 75% yield. Compound **18** was then treated with CBr₄ and PPh₃ to give allyl bromide **19** in 91% yield. After extensive investigation of intramolecular Friedel–Crafts-type reactions of compound **19**, treatment with AgOTf (3.5 equiv.) in 1,2-dichloroethane at room temperature



Scheme 2 Synthesis of ABCD ring model **20** via carboborylation.

for 1 h was found to give the desired ABCD ring model compound **20** in 23% yield with 7:1 diastereoselectivity. The newly generated major diastereomer was confirmed to have the desired stereochemistry using NOESY experiments. Adding 10 mol% Bi(OTf)₃ was also effective,¹⁶ affording compound **20** in 32% yield along with a byproduct¹⁷ in 45% yield. This byproduct was produced by over-reaction of the desired product. Therefore, the reaction time was shortened from 1 h to 20 min. The desired ABCD ring model compound **20** was successfully obtained in 49% yield as the major product (7:1 dr) by reducing the byproduct (30% yield). Resulting product **20** would be useful for further investigations because it contains several convertible functional groups, including olefin, protected amine, and methoxy groups.

In summary, we have developed an intramolecular carboborylation of 1,3-dienes bearing a carbodiimide group for the synthesis of iminoindolines with a quaternary carbon centre. This reaction could be applied to complex substrate **16** bearing methoxy, pNs, and Cbz groups. Furthermore, the obtained iminoindoline **17** was converted to model tetracyclic ABCD ring compound **20**, which comprises the partial structure of communesins, through an intramolecular Friedel–Crafts-type reaction. Investigations into the transformation of this tetracyclic compound toward the total synthesis of communesins are underway in our laboratory.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

This work was supported by a Grant-in-Aid from JSPS KAKENHI (Grant Nos. JP17H05051 (CT) and JP16H06384 (YT)) and the Platform Project for Supporting Drug Discovery and Life Science Research from the Japan Agency for Medical Research and Development (AMED).

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